

Pre-natal exposure to paracetamol and risk of wheezing and asthma in children: A birth cohort study

Cristina Rebordosa,^{1,2,3,4*} Manolis Kogevinas,^{1,2,4,5} Henrik T Sørensen^{6,7} and Jørn Olsen^{8,9}

Accepted 17 March 2008

Background Paracetamol use has been associated with increased prevalence of asthma in children and adults, and one study reported an association between pre-natal exposure to paracetamol and asthma in early childhood.

Methods To examine if pre-natal exposure to paracetamol is associated with the risk of asthma or wheezing in early childhood, we selected 66 445 women from the Danish National Birth Cohort for whom we had information on paracetamol use during pregnancy and who participated in an interview when their children were 18-months-old and 12 733 women whose children had reached the age of 7 and estimated the prevalence of physician-diagnosed asthma and wheezing at the ages of 18 months and 7 years. We also linked our population to the Danish National Hospital Registry to record all hospitalizations due to asthma up to age of 18 months.

Results Paracetamol use during any time of pregnancy was associated with a small but statistically significant increased risk of physician-diagnosed asthma or bronchitis among children at 18 months [relative risk (RR)=1.17, 1.13–1.23], hospitalizations due to asthma up to 18 months (hazard ratio=1.24, 1.11–1.38) and physician-diagnosed asthma at 7 years (RR=1.15, 1.02–1.29). The highest risks were observed for paracetamol use during the first trimester of pregnancy and persistent wheezing (wheezing at both 18 months and 7 years) (RR=1.45, 1.13–1.85).

Conclusion Paracetamol use during pregnancy was associated with an increased risk of asthma and wheezing in childhood. If this association is causal, we may need to revisit the clinical practice on use of paracetamol during pregnancy.

Keywords Analgesics, non-steroidal anti-inflammatory drugs, paracetamol, acetaminophen, pregnancy, child development, asthma, wheezing

¹ Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.

² Municipal Institute of Medical Research (IMIM-Hospital del Mar), Barcelona, Spain.

³ Autonomous University of Barcelona, Barcelona, Spain.

⁴ CIBER Epidemiología y Salud Pública (CIBERESP), Spain.

⁵ Medical School, University of Crete, Heraklion, Greece.

⁶ Department of Clinical Epidemiology, Aarhus University Hospital, Denmark.

⁷ Department of Epidemiology, Boston University, MA, USA.

⁸ The Institute of Public Health, University of Aarhus, DK-80000, Aarhus, Denmark.

⁹ Department of Epidemiology, School of Public Health, UCLA, Los Angeles, USA.

* Corresponding author. Centre for Research in Environmental Epidemiology—Municipal Institute of Medical Research, Dr Aiguàder 88, E-08003 Barcelona, Spain.
E-mail: crebordosa@imim.es

Introduction

Paracetamol is frequently used in many populations^{1–2} and an increase in asthma prevalence among paracetamol users has been found in both genders and in different age groups and geographic regions.^{3–7}

The Avon Longitudinal Study of Parents and Children (ALSPAC)^{8–9} found an increased prevalence of wheezing at 30–42 months (OR = 2.10, 95% CI: 1.30–3.41) among children whose mothers used paracetamol ‘most days’ during late pregnancy (20–32 weeks gestational age), and an increased prevalence of asthma at 69–81 months (OR = 1.22, 95% CI: 1.06–1.41) among children whose mothers used paracetamol ‘sometimes’ during late pregnancy. In spite of this paracetamol is believed to have no foetotoxic effects in therapeutic doses and is often the pain reliever of choice during pregnancy.¹⁰ Apparently, the ALSPAC study has not convinced the clinical community and it needs to be corroborated by other data.

A dose-dependent decrease in levels of the antioxidant glutathione in the lungs is a possible mechanism between paracetamol use and asthma^{11–16} but ‘reverse causation’ must also be considered. Some authors suggest that acetylsalicylic acid (aspirin) and other non-steroidal anti-inflammatory drugs (NSAIDs) may be avoided by some asthmatic women^{11–13} and this would lead to artificially increased risks associated with alternative analgesics such as paracetamol.^{3,17,18}

We evaluated the association between paracetamol use during pregnancy (*in utero* exposure) and asthma in children at 18 months and 7 years of age.

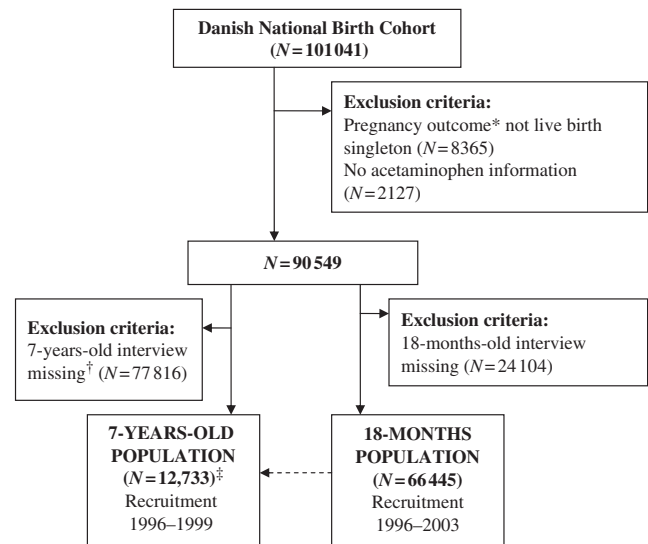
Methods

The Danish National Birth Cohort (DNBC) is a population-based cohort study of approximately 100 000 newborns recruited between 1996 and 2003. Women were asked to complete a self-administered enrolment questionnaire and participate in four telephone interviews (two during pregnancy and two more when the child was 6 months and 18 months of age). Women enrolled early in the study had at the time of our study completed a fifth self-administered questionnaire when the child was 7-years-old. An English version of all the questionnaires can be found at <http://www.bsmb.dk>.¹⁹

From 90 549 women in the cohort who gave birth to a singleton and provided information on paracetamol use during pregnancy, we selected 66 445 women who took part in the 18-month interview and 12 733 mothers who completed a fifth questionnaire when their child reached the age of 7. Among the 12 733 women answering the fifth interview, 9900 had also completed the 18-months interview (Figure 1).

Drug use

Information about paracetamol, aspirin and ibuprofen use was obtained from the interviews. Women were



*Pregnancy outcomes: live birth, stillbirth, miscarriage, induced abortion, hydatidiform mole, ectopic pregnancy, multiple birth, emigrants, mother died and unknown.

[‡]Reasons for not having the 7-years-old interview; being younger than 7-years-old (N = 60067) and lost to follow-up due to death, emigration, not giving the consent or unknown (N = 17749).

[§]Note that the 7 years old population is those mother–child pairs who were recruited initially (1996–1999) in the DNBC and that, at the time of our study, were old enough (7 years) and did answer the 7-years-old interview. From these 12 733 children, 9900 did also the 18-months-old interview, but 2833 did not.

Figure 1 Flow of subjects through the study and selection of the populations

asked for the use of any kind of painkiller and to identify the drugs from a list of 44 specific painkillers including paracetamol available in Denmark. The same procedure was done for drugs used for joint and muscle diseases, inflammations, infections, fever, allergy, asthma and several other diseases. They were also asked to indicate the specific gestational weeks of use, on a week-by-week basis. Duration of exposure was defined as total number of weeks exposed within each trimester. Number of pills per week was only collected in the second and third interview, thus we could not estimate the dose taken in early pregnancy. Information about paracetamol use by the child was obtained from the 6 months- and the 18-months-old interviews; questions were more open and less indication-driven than those asked during pregnancy and not all possible indications for which paracetamol can be used were asked.

Asthma outcomes

When the children were 18-months-old, their mothers were asked if they had ever had wheezing or whistling and if a physician had ever diagnosed them with asthma or bronchitis. At the 7-year interview, the International Study of Asthma and Allergies in Childhood (ISAAC)²⁰ questionnaire was used to get information about their children’s asthma symptoms, physician-diagnosed asthma, ever wheezing or whistling and wheezing or whistling in the past 12 months.

Transient wheezing was defined as occurring only in the first 18 months of life; late onset wheezing as occurring only the past 12 months at the age of 7 years and persistent wheezing as symptoms reported in both time periods. Using Danish residents' unique civil registration numbers to link to the Danish National Hospital Registry we identified all children's hospitalizations due to or with asthma and bronchitis.

Statistical analysis

Poisson regression with robust estimation of error was used to compute cumulative incidence risk ratios for having had physician-diagnosed asthma at 18 months or 7 years and prevalence risk ratios for wheezing in the past 18 months. Cox proportional regression models were used to compute hazard ratios (HR) of hospitalization due to asthma and/or bronchitis up to the age of 18 months. Hereafter, we use the notation relative risk (RR) for all relative effect measures. Follow-up started on the date of birth and ended at the time of the first hospitalization for asthma and/or bronchitis, death, emigration or at 18 months of age, whichever came first. We adjusted for *a priori* selected variables described as asthma risk factors in several other studies, including mother's asthma, gestational age at birth, gender of the child, socio-economic status, duration of breastfeeding, smoking during pregnancy and antibiotic use during pregnancy. An additional list of potential confounders was also evaluated but none of them changed risk estimates (Table 1). Linearity of the association between duration of use and the endpoint was evaluated by using generalized additive models. Statistical analysis was performed with Stata 8.0 software (Stata Corporation, College Station, TX, USA). Ethical approval was obtained from the Ethics Committee for the Municipalities of Copenhagen and Frederiksberg (reference number j. no (KF) 01-471/94).

Results

Socio-demographic and other characteristics of the population are presented in Table 1. Baseline characteristics for the full cohort ($N=90\,549$), the 18 months cohort ($N=66\,445$) and the 7-years-old cohort ($N=12\,733$) were compared and no differences were found between respondents and the full cohort.

Paracetamol was used by 30% ($n=19\,988$) of women from the 18-months-old population during the first trimester of pregnancy, 23% ($n=15\,034$) in the second trimester, 30% ($n=19\,508$) in the third and 54.7% ($n=36\,316$) ever during pregnancy. Similarly, for the 7-years-old population the figures were 3786 (29.8%), 2523 (19.8%) and 3237 (25.4%) and 6752 (53%).

The distribution of asthma-related outcomes is reported in Table 2. The estimated cumulative incidence of physician-diagnosed asthma or bronchitis at 18 months of age was higher than the cumulative

incidence of asthma alone estimated at 7 years of age, probably due to the fact that the question in the 18-month interview included diagnosed asthma and bronchitis, since the two diagnoses are difficult to separate at that age and to a certain degree of recall bias. RRs in Table 2 are shown for each trimester separately. Risk estimates do not change substantially when exposure during a particular trimester is adjusted for exposure in other trimesters (not shown).

Pre-natal exposure to paracetamol was associated with wheezing and asthma both at 18 months and at 7 years of age (Table 2). An increased RR of physician-diagnosed asthma at 7 years of age was associated with paracetamol use during the first and the third trimester and ever use during pregnancy. Paracetamol use during the first trimester was also associated with an increased RR of wheezing in the past 12 months when children were 7-years-old. These estimates changed little when compared with a crude model (no adjustments) or an adjusted model that did not include parental asthma. Compared with the results presented in Table 2, the crude RR of physician diagnosed asthma or bronchitis at 18 months associated to paracetamol exposure ever during pregnancy was $RR=1.23$ (95% CI: 1.19–1.27) and when excluding parental asthma from the fully adjusted model the RR was $RR=1.20$ (95% CI: 1.15–1.24). For physician-diagnosed asthma at 7 years, the crude RR was $RR=1.22$ (95% CI: 1.11–1.34) and the risk when excluding parental asthma was $RR=1.17$ (95% CI: 1.04–1.31).

The highest risk was observed for the association between paracetamol use in the first trimester and persistent wheezing. Persistent wheezing was also associated with paracetamol use during the third trimester; however, after adjusting for exposure during the other trimesters, only paracetamol use in the first trimester remained statistically significant ($RR=1.35$, 95% CI: 1.02–1.78). The crude estimate for persistent asthma associated to paracetamol exposure during the first trimester was $RR=1.47$ (95%CI: 1.20–1.80) and the estimate excluding only parental asthma from the fully adjusted model was $RR=1.41$ (95% CI: 1.10–1.81). A subgroup of mothers used paracetamol only in the first trimester and the asthma risk for their children was $RR=1.50$, (95% CI: 1.02–2.21), compared with unexposed children during their entire pregnancy.

Use of paracetamol during pregnancy was associated with an increase in the rate of hospitalizations up to 18 months of age for asthma ($HR=1.24$, 95% CI: 1.11–1.38) and asthma or bronchitis ($HR=1.22$, 95% CI: 1.10–1.36) (Table 2), but not for hospitalizations due to bronchitis only ($HR=1.08$, 95% CI: 0.74–1.56).

The association between paracetamol use during pregnancy and wheezing at 18 months ($RR=1.14$, 95% CI: 1.10–1.17) remained statistically significant when we restricted the analysis to children who had been exposed to the drug only during pregnancy. Information on use of paracetamol by the child after

Table 1 Socio-demographic characteristics of the population and potential confounders evaluated and finally included in the analysis^a

	Whole population (<i>N</i> = 90 459) <i>n</i> (%)	18-months-old population (<i>N</i> = 66 455) <i>n</i> (%)	7-years-old population (<i>N</i> = 12 733) <i>n</i> (%)
Paracetamol use during pregnancy			
1st trimester	26 945 (29.8)	19 988 (30.1)	3786 (29.7)
2nd trimester	20 290 (22.4)	15 034 (22.6)	2523 (19.8)
3rd trimester	25 701 (28.4)	19 508 (29.4)	3237 (25.4)
Ever during pregnancy	49 029 (54.2)	36 316 (54.7)	6752 (53.0)
Potential confounders included			
Child's sex			
Female	44 122 (48.8)	32 552 (49.0)	6167 (48.5)
Male	46 341 (51.2)	33 864 (51.0)	6555 (51.5)
Socio-economic status ^b			
High	57 734 (66.8)	43 279 (67.7)	8303 (67.3)
Medium	25 236 (29.2)	18 421 (28.8)	3585 (29.1)
Low	3480 (4.0)	2234 (3.5)	445 (3.6)
Mother ever had asthma	8507 (9.4)	6041 (9.1)	1092 (8.6)
Father ever had asthma	7107 (8.3)	5204 (8.2)	926 (7.5)
Maternal smoking during pregnancy (cigarettes/day)			
Never	66 721 (73.7)	49 732 (74.9)	9460 (74.3)
<6	13 073 (14.4)	8968 (13.5)	1765 (13.9)
Six or more	10 715 (11.8)	7734 (11.6)	1506 (11.8)
Mother used antibiotics during pregnancy	18 236 (20.1)	13 505 (20.3)	2732 (21.5)
Gestational age at birth (days)			
<258	4067 (4.5)	2801 (4.2)	497 (3.9)
259–293	78 006 (86.5)	57 523 (86.9)	10 990 (86.9)
294 or more	8096 (9)	5882 (8.9)	1163 (9.2)
Duration of breastfeeding (months)			
None	45 243 (64.7)	35 839 (65.3)	5740 (64.3)
1–4	11 438 (16.4)	8704 (15.9)	1295 (14.5)
4 or more	13 248 (18.9)	10 358 (18.9)	1892 (21.2)
Other potential confounders evaluated			
Mother age (years)			
<24	8670 (9.6)	5525 (8.3)	1059 (8.3)
25–29	34 853 (38.6)	25 601 (38.6)	4732 (37.3)
30–35	33 495 (37.1)	25 076 (37.8)	5041 (39.7)
36 or more	13 360 (14.8)	10 147 (15.3)	1864 (14.7)
Birth order			
First	40 701 (46.9)	29 448 (45.9)	5232 (42.3)
Mother had fever during pregnancy	24 861 (27.5)	18 084 (27.3)	3879 (30.5)
Mother had muscle or joint disease during pregnancy	15 169 (16.8)	11 184 (16.9)	2406 (18.9)
Mother had inflammation or infection during pregnancy	12 439 (14.1)	9406 (14.3)	1877 (14.9)
Mother had hypertension during pregnancy	10 189 (11.6)	7716 (11.8)	1259 (10.0)
Mother ever had allergy	27 546 (30.9)	20 323 (30.8)	3820 (30.5)
Mother ever had eczema	7108 (12.3)	7108 (12.3)	628 (11.1)
Pets during the first 18 months of live	37 463 (56.4)	37 463 (56.4)	5424 (54.8)
Alcohol consumption during pregnancy ^c (glasses/day)			
None	52 498 (58.1)	37 814 (57.0)	7271 (57.1)
One	23 582 (26.1)	17 596 (26.5)	3358 (26.4)
Two or more	14 351 (15.9)	10 962 (16.5)	2096 (16.5)

^aNumbers (percentages) do not sum due to missing values.^bMother socio-economic status is a composed variable derived from the mother's and father's educational level and occupation.^cIncludes beer, wine, spirits and equivalences are done as 1 glass = 12 g.

Table 2 RR for asthma at 18 months and 7 years of age according to pre-natal exposure to paracetamol

	<i>n</i> dis (%)	Paracetamol use during pregnancy									
		1st trimester			2nd trimester			3rd trimester			Ever
		<i>n</i> exp	RR ^a (95% CI)	<i>n</i> exp	RR ^a (95% CI)	<i>n</i> exp	RR ^a (95% CI)	<i>n</i> exp	RR ^a (95% CI)		
18-month-old population (<i>N</i> = 66 445)^b											
Physician-diagnosed asthma/bronchitis (<i>n</i> = 66 079)	11 476 (17.4)	3847	1.15 (1.10–1.19)	2928	1.13 (1.09–1.18)	3857	1.17 (1.13–1.22)	6852	1.18 (1.13–1.23)		
Wheezing ever (<i>n</i> = 66 373)	17 805 (26.8)	5788	1.11 (1.08–1.14)	4350	1.09 (1.05–1.12)	5641	1.10 (1.06–1.13)	10 358	1.13 (1.10–1.17)		
Hospitalization for asthma (<i>n</i> = 66 445)	1757 (2.6)	599	1.17 (1.05–1.30)	468	1.20 (1.07–1.36)	609	1.18 (1.05–1.31)	1085	1.24 (1.11–1.38)		
7-year-old population (<i>N</i> = 12 733)											
Physician-diagnosed asthma (<i>n</i> = 12 530)	1530 (12.1)	504	1.15 (1.01–1.29)	333	1.06 (0.92–1.22)	448	1.17 (1.04–1.32)	886	1.15 (1.02–1.29)		
Wheezing in the last 12 months (<i>n</i> = 11 998)	960 (8.0)	323	1.29 (1.11–1.51)	194	1.03 (0.86–1.24)	264	1.02 (0.87–1.20)	543	1.16 (0.99–1.35)		
Transient wheezing (<i>n</i> = 8623)	2722 (31.6)	832	1.06 (0.98–1.15)	568	1.05 (0.96–1.15)	762	1.10 (1.01–1.18)	1500	1.07 (1.00–1.16)		
Persistent wheezing (<i>n</i> = 6272)	371 (5.9)	129	1.45 (1.13–1.85)	83	1.24 (0.94–1.65)	126	1.33 (1.03–1.70)	228	1.37 (1.07–1.75)		
Late onset wheezing (<i>n</i> = 6240)	339 (5.4)	114	1.25 (0.97–1.61)	60	0.91 (0.66–1.24)	869	0.90 (0.69–1.17)	187	1.15 (0.91–1.47)		

^aRR were adjusted by parental asthma, gender of the child, social class, gestational age, breastfeeding, tobacco exposure during pregnancy and antibiotic use during pregnancy.

^b*N* indicates the total number of subjects, *n* the number of subjects for whom we have information for each outcome, *n* dis the number of individuals having the disease and *n* exp is the number of exposed subjects among those who have the disease.

birth was completed by a small percentage of the population and indicated that use of paracetamol both pre- and post-natally (RR = 1.3, 95% CI: 1.19–1.44) was associated with a higher risk than only post-natal use (RR = 1.22, 95% CI: 1.07–1.38). Similar results were obtained for physician-diagnosed asthma/bronchitis.

There was no general pattern of asthma risk associated with use of aspirin or ibuprofen ever during pregnancy (Table 3) neither for use in specific trimesters.

Pain was the main reason for paracetamol use. Among the 49 029 women who reported having taken paracetamol during pregnancy, 44 139 (91%) answered that they used paracetamol when asked for drugs taken for pain, 15 897 (32%) when they were asked for fever, 7900 (16%) when they were asked for infection or inflammation and 9591 (20%) when they were asked for drugs taken for muscle or joint diseases. Most women that used paracetamol for pain also reported use for other indications. Only 8725 women (18%) used paracetamol only for fever without pain, 5578 (11%) only for infection or inflammation and 4318 (9%) only for muscle or joint diseases. Adjusting the models for indication of use did not modify the risk estimates for paracetamol use nor did the estimates change when stratifying for indication of use. No effect modification or interaction was seen, except for a small increase of the risk associated with use of paracetamol when the indication of use was inflammation or infection (RR = 1.30, 95% CI 1.17–1.44). When stratifying by antibiotics use, (that have also been implicated in children's asthma), those women who had inflammation or infection but did not use antibiotics had an increased risk of physician diagnosed asthma at 18 months (RR = 1.26, 95% CI 1.07–1.48) that was slightly lower than the risk for those who used antibiotics (RR = 1.38, 95% CI 1.16–1.52).

Since confounding by indication is also expected to be present for other pain killers, we examined children exposed to these drugs. Risks for wheezing and for physician-diagnosed asthma at 18 months among children whose mothers took only paracetamol during pregnancy were similar to those whose mother took both paracetamol and aspirin (Table 4). In contrast, risks were lower for children whose mothers took only aspirin. Results were similar for asthma and wheezing at 7 years of age.

Use of paracetamol during the first trimester was associated with severity of asthma attacks at 7 years of age, measured as the number of wheezing attacks affecting sleep. Compared with children who never woke up with wheezing in the last 12 months, a statistically significant increased risk was observed for wheezing attacks affecting sleep less than once a week (RR = 1.27, 95% CI: 1.03–1.57) and for wheezing attacks affecting sleep one or more nights per week (RR = 1.68, 95% CI: 1.06–2.66) (see Supplementary Table S5 available at *IJE* online).

Total number of weeks of paracetamol use during the entire pregnancy, or weeks of use within specific

Table 3 Relative measures of association (RR) for asthma at 18 months and 7 years of age according to pre-natal exposure to aspirin and ibuprofen

	Aspirin		Ibuprofen	
	<i>n</i> exp	RR ^a (95% CI)	<i>n</i> exp	RR ^a (95% CI)
18-month-old population (<i>N</i> = 66 445)^b				
Physician-diagnosed asthma/bronchitis	807	0.93 (0.87–1.00)	631	1.04 (0.96–1.13)
Wheezing ever	1388	1.02 (0.97–1.08)	961	1.04 (0.98–1.11)
Hospitalization for asthma	125	0.99 (0.81–1.21)	106	1.07 (0.85–1.34)
7-year-old population (<i>N</i> = 12 733)				
Physician-diagnosed asthma	125	0.83 (0.68–1.03)	79	1.02 (0.79–1.33)
Wheezing in the last 12 months	86	0.88 (0.67–1.15)	50	1.25 (0.91–1.71)
Transient wheezing	282	1.02 (0.91–1.15)	146	1.17 (1.00–1.36)
Persistent wheezing	34	0.81 (0.51–1.28)	17	1.42 (0.87–2.31)
Late onset wheezing	33	0.99 (0.67–1.48)	12	0.76 (0.38–1.52)

^aRR were adjusted by parental asthma, gender of the child, social class, gestational age, breastfeeding, tobacco exposure during pregnancy and antibiotic use during pregnancy.

^b*N* indicates the total number of subjects and *n* exp is the number of exposed subjects among those who have the disease.

Table 4 Relative risks (RR) for physician-diagnosed asthma/bronchitis and wheezing at 18 months according to pre-natal exposure to paracetamol and/or aspirin

18-months-old population (<i>N</i> = 66 445)					
APAP ^a	AAS ^a	<i>n</i> (%)	Doctor-diagnosed asthma RR ^b (95% CI)	Wheezing ever up to 18-months-old RR ^b (95% CI)	
1st trimester					
No	No	43 840 (66.0)	1 (ref)	1 (ref)	
Yes	No	18 960 (28.5)	1.15 (1.10–1.19)	1.11 (1.08–1.14)	
No	Yes	2617 (3.9)	0.94 (0.84–1.04)	1.04 (0.96–1.12)	
Yes	Yes	1028 (1.6)	1.08 (0.94–1.25)	1.15 (1.04–1.28)	
2nd trimester					
No	No	50 326 (75.7)	1 (ref)	1 (ref)	
Yes	No	14 727 (22.2)	1.13 (1.08–1.18)	1.09 (1.05–1.12)	
No	Yes	1085 (1.6)	0.99 (0.85–1.16)	1.02 (0.91–1.14)	
Yes	Yes	307 (0.5)	1.24 (0.97–1.58)	1.17 (0.97–1.41)	
3rd trimester					
No	No	46 154 (69.5)	1 (ref)	1 (ref)	
Yes	No	19 109 (28.8)	1.17 (1.13–1.22)	1.10 (1.06–1.13)	
No	Yes	783 (1.2)	0.92 (0.77–1.10)	1.05 (0.92–1.19)	
Yes	Yes	399 (0.6)	1.10 (0.89–1.36)	1.21 (1.04–1.40)	
Ever					
No	No	27 878 (42.0)	1 (ref)	1 (ref)	
Yes	No	33 556 (50.5)	1.19 (1.14–1.24)	1.15 (1.11–1.18)	
No	Yes	2251 (3.4)	1.00 (0.89–1.12)	1.10 (1.02–1.20)	
Yes	Yes	2760 (4.2)	1.06 (0.96–1.17)	1.11 (1.03–1.19)	

^aAPAP stands for paracetamol and AAS for acetylsalicylic acid (aspirin).

^bAdjusted by parental asthma, gender of the child, social class, gestational age, breastfeeding, tobacco exposure during pregnancy and antibiotic use during pregnancy.

trimesters, was not associated with a higher probability of having a child with asthma or wheezing at the age of 7 years (data not shown).

Discussion

Children pre-natally exposed to paracetamol had a slightly increased risk of wheezing and physician-diagnosed asthma at 18 months and at 7 years of age, especially for use of paracetamol during the first trimester of pregnancy and asthma and wheezing at the age of 7. Also, pre-natal exposure to paracetamol was associated with an increased risk of hospitalization due to asthma. These associations did not appear to be confounded by indication for mothers' use nor by post-natal paracetamol use or by parental asthma risk. Similar associations were not seen for pre-natal exposures to other painkillers.

Our data corroborate the findings made in the ALSPAC cohort but we also found discrepancies. Our data indicate the highest risk to be associated with first trimester exposure and not third trimester exposure as the ALSPAC^{9–10} study suggests and our associations were lower than those reported by the ALSPAC study.

Although the findings were robust in our analysis, we cannot rule out uncontrolled confounding a possible explanation of the association. The lack of a dose response effect is probably less important, since timing of exposure is often more important than the dose during pregnancy.

Paracetamol crosses the placenta and the observed increased risk may be related to the limited capacity of the foetus to metabolize paracetamol. In adults, the main detoxification pathway of paracetamol is glucuronidation to the non-toxic metabolite glucuronide, while in the foetus the main metabolic pathway initially involves sulphation. Glucuronidation starts at the 18th gestational week and increases until the 23rd

week-a pattern that could be related to an increased risk from exposure in the first trimester.²¹ Metabolism of paracetamol to the highly reactive oxide *N*-acetyl-*p*-benzoquinoneimine (NAPQI), depends on the activity of the cytochrome P450 system and on Glutathione S Transferase (GST). In adults, cytochrome P450 enzymes metabolize 4–5% of the paracetamol to NAPQI, and this percentage increases when glucuronidation and sulphation are saturated.^{21,22} NAPQI is then detoxified by GST. The expression of GST in the lung of the foetus progressively decreases after week 15 of gestation, and this could be related to an increase in risk from use of paracetamol in the third trimester.^{23,24}

A paracetamol dose-dependent decrease in levels of the anti-oxidant glutathione in the lung has been proposed. Recent studies^{25–27} suggest that glutathione depletion in the lung may occur in relatively low doses. This may reduce the capacity to counteract the toxic effects of NAPQI and may affect the response to oxidative stress and possibly also to impaired antigen processing.

Avoiding NSAIDs may exert an effect on the lungs mediated by the lack of suppression of COX, an anti-inflammatory pathway that promotes prostaglandin E2 production in favour of T-helper type 2 response while inhibiting T-helper type 1 lymphocytes. This would promote an allergic tendency in the immune response to various antigenic stimuli. Yet, another possible mechanism is an immune-modulating IgE mediated effect of paracetamol as an antigenic agent, which would increase asthma provocation.^{11–16,28}

Among the potential biases affecting our results, differential exposure misclassification is unlikely since the reported drug use was recorded before birth. Outcome misclassification is present to some extent but is hardly influenced by pre-natal exposure to a common drug that it is not well known to have a potential effect on asthma, and two different data sources provided consistent estimates of asthma prevalence. Women with asthma might be more likely to take paracetamol instead of aspirin or other NSAIDs, but our estimates did not change when we adjusted for indications for its use, mother's history of allergy or eczema, nor did we see any associations for other painkillers used for similar indications.

An important limitation of our study is the limited data we have on post-natal drug use in children. Risks for pre-natal exposure to paracetamol were similar after adjustment for children's use of paracetamol reported to the first 18 months of age. However, the reported

prevalence of use of paracetamol up to 18 months of age is much lower than what is described in other studies^{29,30} and might be underreported due to incomplete exposure assessment.

Possible adverse effects related to the use of paracetamol in pregnancy need further investigation, especially regarding the possible duration of an effect and the importance of combined pre-natal and post-natal exposures.

Pre-natal exposure to paracetamol may be one of several causes of asthma. Although the associations we found were moderate, the health consequences may well be important due to the frequent use of this drug during pregnancy and the high prevalence of asthma in childhood. Long term health consequences of drug use during pregnancy for the offspring should always be considered.

Supplementary data

Supplementary data are available at *IJE* online.

Acknowledgements

We acknowledge Inge Eiseensee (Danish Epidemiology Science Centre, University of Aarhus) for dataset preparation and Estel Plana (Centre for Research in Environmental Epidemiology) for her support in data management and analysis. We are especially grateful to the physicians, nurses, interviewers and mothers without whose participation the study would not have been possible. This work was funded by the Danish National Research Foundation has established the Danish Epidemiology Science Centre that initiated and created the Danish National Birth Cohort. The cohort is, furthermore, a result of a major grant from this Foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation and the Health Foundation. C.R. was partly supported by the Spanish Ministry of Health (Carlos III Institute, ISCIII-CM06/00118) and by the European Union Sixth Framework Program (FP6-2003-Food-3-A), and this article will be part of her PhD thesis at the Autonomous University of Barcelona. The authors work was independent of the funders.

Conflict of interest: None declared.

KEY MESSAGES

- Paracetamol use during pregnancy is associated with an increased risk of asthma and wheezing in childhood.
- The findings of this prospective study support the hypothesis that childhood asthma may begin *in utero*.
- The public health consequences of these findings may be important due to the frequent use of paracetamol during pregnancy and the high prevalence of asthma in childhood.

References

- ¹ Headley J, Northstone K, Simmons H, Golding J. ALSPAC Study Team. Medication use during pregnancy: data from the Avon Longitudinal Study of parents and children. *Eur J Clin Pharmacol* 2004;**60**:355–61.
- ² Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. *Am J Obstet Gynecol* 2005;**193**:771–77.
- ³ Barr RG, Wentowski CC, Curhan GC *et al.* Prospective Study of Acetaminophen use and newly diagnosed asthma among women. *Am J Respir Crit Care Med* 2004;**169**:836–41.
- ⁴ Newson RB, Shaheen SO, Chinn S, Burney PGJ. Paracetamol sales and atopic disease in children and adults: an ecological analysis. *Eur Respir J* 2000;**16**:817–23.
- ⁵ Shaheen SO, Sterne JAC, Songhurst CE, Burney PGJ. Frequent paracetamol use and asthma in adults. *Thorax* 2000;**55**:266–70.
- ⁶ McKeever TM, Lewis SA, Smit HA, Burney P, Britton JR, Cassano PA. The Association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. *Am J Respir Crit Care Med* 2005;**171**:966–71.
- ⁷ Davey G, Berhane Y, Duncan P, Aref-Adib G, Britton J, Venn A. Use of acetaminophen and the risk of self-reported allergic symptoms and skin sensitization in Butajira, Ethiopia. *J Allergy Clin Immunol* 2005;**116**:863–68.
- ⁸ Shaheen SO, Newson RB, Sherriff A *et al.* Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002;**57**:958–63.
- ⁹ Shaheen SO, Newson RB, Henderson AJ *et al.* Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy* 2005;**35**:18–25.
- ¹⁰ Rathmell JP, Viscomi CM, Ashburn MA. Management of nonobstetric pain during pregnancy and lactation. *Anesth Analg* 1997;**85**:1074–87.
- ¹¹ Allmers H. Frequent acetaminophen use and allergic diseases: is association clear? *J Allergy Clin Immunol* 2005;**116**:859–62.
- ¹² Nuttall SL, Williams J, Kendall MJ. Does paracetamol cause asthma? *J Allergy Clin Immunol* 2003;**28**:251–57.
- ¹³ Eneli I, Sadri K, Camargo C Jr, Barr RG. Acetaminophen and risk of asthma: the epidemiologic and pathophysiologic evidence. *Chest* 2005;**127**:604–12.
- ¹⁴ Fogarty A, Davey G. Paracetamol, antioxidants and asthma. *Clin Exp Allergy* 2005;**35**:700–02.
- ¹⁵ Dimova S, Hoet PHM, Dinsdale D, Nemery B. Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes in vitro. *IJBCB* 2005;**37**:1727–37.
- ¹⁶ Dimova S, Hoet PHM, Nemery B. Paracetamol (acetaminophen) cytotoxicity in rat type II pneumocytes and alveolar macrophages in vitro. *Biochem Pharmacol* 2000;**59**:1467–75.
- ¹⁷ Lesko SM, Mitchell AA. The Safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics* 1999;**104**:39–43.
- ¹⁸ Lesko SM, Louik C, Vezina RM, Mitchell AA. Asthma morbidity after short-term use of ibuprofen in children. *Pediatrics* 2002;**109**:20–23.
- ¹⁹ Olsen J, Melbye M, Olsen SF *et al.* The Danish National Birth Cohort—its background, structure and aim. *Scand J Public Health* 2001;**29**:300–7.
- ²⁰ The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998;**12**:315–35.
- ²¹ Wilkes JM, Clark LE, Herrera JL. Acetaminophen overdose in pregnancy. *South Med Assoc* 2005;**98**:1118–22.
- ²² Klaassen CD. *Cassarett, & Doull's: Toxicology. The basic science of poisons*. 6th edn. NY: Mc Graw-Hill, 2001.
- ²³ Fryer AA, Hume R, Strange RC. The development of glutathione S-transferase and glutathione peroxidase activities in human lung. *Biochim Biophys Acta* 1986;**883**:448–53.
- ²⁴ Cossar D, Bell J, Strange R, Jones M, Sandinson A, Hume R. The alpha and pi isoenzymes of glutathione S-transferase in human fetal lung: in utero ontogeny compared with differentiation in lung organ culture. *Biochim Biophys Acta* 1990;**1037**:1467–75.
- ²⁵ Ludmir J, Main DM, Landon MB, Gabbe SG. Maternal acetaminophen overdose at 15 weeks of gestation. *Obstet Gynecol* 1986;**67**:750–51.
- ²⁶ Nuttall SL, Khan JN, Thorpe GH, Path FRC, Langford N, Kendall MJ. The impact of therapeutic doses of paracetamol on serum total antioxidant capacity. *J Clin Pharm Ther* 2003;**28**:289–94.
- ²⁷ Rollins DE, von Bahr C, Glaumann H, Moldens P, Rane A. Acetaminophen: potentially toxic metabolite. *Science* 1979;**205**:1414–16.
- ²⁸ Wong ICK, Furnes J, MacDonald F *et al.* Paracetamol and asthma. *Thorax* 2000;**55**:882–4.
- ²⁹ Headley J, Northstone K. Medication administered to children from 0 to 7.5 years in the Avon Longitudinal Study of Parents and Children (ALSPAC). *Eur J Clin Pharmacol* 2007;**63**:189–95.
- ³⁰ Walsh A, Edwards H, Fraser J. Over-the-counter medication use for childhood fever: A cross-sectional study of Australian parents. *J Paediatr Child Health* 2007;**43**:601–6.

Supplemental table, online only

Supplemental Table 5. Use of paracetamol during pregnancy and child's wheezing attacks during the last 12 months and wheezing attacks affecting sleep at age 7.

	Number of wheezing attacks in the last 12 months*				Number of wheezing attacks affecting sleep in the last 12 months*			
	1 to 3		4 or more		<1/week		1 or more/week	
	<i>RR</i> [†]	95% <i>CI</i>	<i>RR</i> [†]	95% <i>CI</i>	<i>RR</i> [†]	95% <i>CI</i>	<i>RR</i> [†]	95% <i>CI</i>
Paracetamol								
1st trim	1.28	(1.08- 1.53)	1.20	(0.83- 1.75)	1.27	(1.03- 1.57)	1.68	(1.06- 2.66)
2nd trim	0.97	(0.79- 1.20)	1.32	(0.88- 1.99)	0.95	(0.73- 1.22)	1.76	(1.09- 2.84)
3rd trim	1.04	(0.87- 1.25)	1.05	(0.71- 1.54)	1.09	(0.88- 1.36)	0.97	(0.60- 1.59)
ever	1.14	(0.96- 1.35)	1.22	(0.85- 1.75)	1.21	(0.99- 1.49)	1.13	(0.71- 1.80)

*Reference is no wheezing attacks in the last 12 months (RR=1.00).

†Adjusted by parental asthma, gender of the child, social class, gestational age, breastfeeding, tobacco exposure during pregnancy and antibiotic use during pregnancy.